GPhA
Generic Pharmaceutical Association

1620 I Street, NW • Suite 800 • Washington, DC 20006
202-833-9070 • Fax: 202-833-9612 • Email: info@gphaonline.org

January 28, 2002

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane
Room 1061 – HFA-305
Rockville, MD 20852

Re: Docket No. 01D-0488 Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling, October, 2001

Dear Madam or Sir:

On behalf of the Generic Pharmaceutical Association (GP*h*A), I submit the following comments on the Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling, October, 2001, Docket No. 01D-0488.

Lines 67-68

Food effects on BA are generally greatest when the drug product is administered immediately after a meal is ingested.

Comments:

We are not sure whether taking a drug product immediately after a meal is ingested or in the middle of a meal results in less "food effect" on BA. For consistency in study design, we recommend the following:.

Food effects on BA of the drug product should be determined shortly after a meal is ingested.

Lines 236-237

The meal should be consumed over 30 minutes with administration of the drug product immediately after the meal.

01D-0488

C10

Comments:

Since study subjects eat at different rates, some of the subjects will finish their meal in less than 30 minutes. This small variability in time for food consumption should not impact the study. To coordinate meal consumption and administration of the drug product, we propose:

The meal should be started 30 minutes prior to the administration of the drug product. Study subjects must eat their meal within 30 minutes, drug will be administered 30 minutes after the start of the meal.

Lines 259-268

The following exposure measures for assessment of BA and BE should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- *Total exposure, or area under the concentration-time curve ($AUC_{0-\infty}$ AUC_{0-t})*
- *Peak exposure (C_{max})*
- *Time to peak exposure (T_{max})*
- *Lag-time (t_{lag}) for modified-release products, if present*
- *Terminal elimination half-life*
- *Other relevant pharmacokinetic parameters*

Comment:

All of these measures are not relevant to define BA or BE. Some of the measures are not robustly obtainable using the same pharmacokinetic methodology. For example, the lag-time (t_{lag}) parameter can only be robustly assessed using compartmental PK approaches.

The purpose of a BE study is to compare two formulations in terms of rate and extent of bioavailability. In pharmacokinetics, these processes are described by the parameters K_a (absorption rate constant) and F (bioavailability). Individual pharmacokinetic analysis using compartmental methods is very susceptible to noise in a data set. Estimation of the parameters, AUC (metric for extent of bioavailability) and C_{max} (metric for rate of bioavailability) by noncompartmental analysis is robust and simple in most cases. We recommend that the PK parameters should only include those that can be robustly calculated by noncompartmental methods:

- C_{max}
- T_{max}
- AUC_{0-t}
- $AUC_{0-\infty}$
- K_{el}

The parameters to pass bioequivalence should be limited to C_{max} (indicative of rate of bioavailability) and AUC (indicative of extent of bioavailability) using the noncompartmental approach.

Lines 315-317

For an ANDA, BE of a test product to the RLD product under fed conditions is concluded when the 90% CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80-125% for AUC and C_{max}.

Comments:

ANDAs have been approved and marketed over the last ten years with no documented safety issues. Food effect studies have been approved for these ANDAs with point estimate acceptance criteria. The demonstrated safety and wide acceptance of these products by the general public are indicative of the robustness and adequacy of the current approval process. Rather than the confidence intervals in the current draft guidance, we propose maintaining the system as it is applied today.

Comments on AUC_{0-t} and $AUC_{0-\infty}$:

Passing on both the AUC_{0-t} and $AUC_{0-\infty}$ should not be a strict criteria in a bioequivalence study. AUC_{0-t} will be reflective of the $AUC_{0-\infty}$ and an appropriate criteria for BE in the following circumstances:

- The PK has been correctly assessed (the observed AUC_{0-t} should be on average 90% or more of the $AUC_{0-\infty}$).
- All collected samples are above the lower limit of quantification of the analytical method. If the latter is not true, then asking to pass on AUC_{0-t} can be flawed scientifically. For example, one can end up comparing AUC_{0-36} with AUC_{0-24} within subjects in a crossover study.
- For some cases, the extrapolation of the terminal elimination half-life that is needed to estimate $AUC_{0-\infty}$ is unobtainable in some of the study subjects. This may be the case for transdermal and extended release drug products.

Lines 317-318

Although no criterion applies to T_{max}, the T_{max} values for the test and reference products are expected to comparable based on clinical relevance.

GPhA
Generic Pharmaceutical Association

Comments:

The term, "comparable" is vague and tends to be subjective. We feel that the T_{max} should be provided for information purposes only.

We appreciate your consideration of our comments. Please contact me, if you have any questions or need clarification.

Respectfully submitted,

Steve Bende, Ph.D.
Vice President
Science, Professional and Regulatory Affairs

Generic Pharmaceutical Association
1620 I (Eye) St., NW
Suite 800
(202) 833-9070
(202) 833-9612 fax

GPhA
Generic Pharmaceutical Association

Fax

To:	FDA Dockets Management Branch	**From:**	Steve Bende, Ph.D.
Fax:	301-827-6870	**Pages:**	4 plus cover = 5
Phone:	301-827-6860	**Date:**	1/28/2002
Re:	Docket Submission	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Attached please find the comments of the Generic Pharmaceutical Association regarding Docket No. 01D-0488. The comments are being FedEx-ed as well for your receipt tomorrow.

Thank you

Steve Bende, Ph.D.
Vice President
Science, Professional and Regulatory Affairs